adata, citation and similar papers at core.ac.uk
brought to you by
provided by Helsingin yliopiston digita

Pharmaceutical Technology Division
Finland

Aqueous-based amylose-rich maize starch solution and dispersion: a study on free films and coatings

Karin Krogars

Academic Dissertation

To be presented, with the permission of
the Faculty of Science of the University of Helsinki, for public criticism
in Auditorium 1041 of Viikki Biocentre,
on November 8th, 2003 at 12 noon

Helsinki 2003

Supervisors

Docent Jyrki Heinämäki
Pharmaceutical Technology Division
Department of Pharmacy
University of Helsinki

Professor Jouko Yliruusi
Pharmaceutical Technology Division
Department of Pharmacy
University of Helsinki

Reviewers

Dr. Kirsi Jouppila
Department of Food Technology
University of Helsinki

Professor Jouni Hirvonen
Pharmaceutical Technology Division
Department of Pharmacy
University of Helsinki

Opponent

Professor Kristiina Järvinen
Department of Pharmaceutics
University of Kuopio

© Karin Krogars 2003
ISBN 952-10-1055-X
ISBN 952-10-1056-8 (PDF)
ISSN 1239-9469

Helsinki University Printing House
Helsinki 2003
Finland

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

The work was carried out in the Pharmaceutical Technology Division, Department of Pharmacy, University of Helsinki, during the years 1999-2003.

I would like to express my sincere gratitude to my supervisors: to Professor Jouko Yliruusi for his open-minded scientific thinking, encouragement and interest in my work and for scientific guidance during these years and to Docent Jyrki Heinämäki for always finding time for my problems, for constructive criticism and for sharing, his scientific experience, particularly his knowledge of film coating.

Dr. Kirsi Jouppila and Professor Jouni Hirvonen are thanked for their careful examination of this thesis and constructive comments on the text.

I am deeply indebted to my co-authors: to Osmo Antikainen for sharing his experience in statistical analysis, to Docent Milja Karjalainen for guidance in X-ray diffraction analysis, and to Docent Jukka Rantanen, Dr. Niklas Laitinen and Dr. Pirjo Luukkonen for their valuable scientific contributions. Professor Markku Leskelä and Antti Niskanen are thanked for constructive comments on the manuscript.

I am most grateful to my colleagues in the Pharmaceutical Technology Division for providing a pleasant working atmosphere (something similar will be hard to find). In particular I would like to thank Dr. Pirjo Luukkonen for our many work-related discussions but also for her friendship outside of work. Special thanks go to Sari Airaksinen and Dr. Hongxia Guo for being great office mates.

My friends were a wonderful support. The friendships with Anne Lindblom, Ylva Eriksson, Ancki Laitinen, Lotta Lehtola, Janita Metsämäki and Carina Grönholm have lasted over two decades now and our discussions about everything but pharmaceutical technology are always a source of stimulation and enjoyment.

I warmly thank my parents Margareta and Jarl and my brother Dan for their loving support and for always offering a helping hand when needed.

Most of all I thank Jan-Patrik for his love, encouragement and most valuable support and my dear children, Alice and Mikael, for an abundance of joyful moments.

Porvoo, October 2003

ABSTRACT

Starch is widely used as a binder and filler, but it has not so far been used as a coating agent for pharmaceutical dosage forms. This biopolymer has good film forming ability, but it also has limitations related to its tendency to age during storage through migration of plasticizers and degeneration of mechanical properties. Moreover, aqueous based coatings are preferred for pharmaceutical purposes and starch is not soluble in water at ambient temperature.

The aim of the study was to investigate the possibility of using amylose-rich maize starch as a coating agent for pharmaceutical purposes. The study comprised the preparation of free films and coatings from (A) heated solution and (B) ambient tempered dispersion. In the case of solution, study was made of the stability of free films plasticized with sorbitol and glycerol separately and in combination and of the effect of plasticizer content and coating process conditions on the resultant coatings. A new film forming ambient tempered amylose-rich maize starch dispersion was developed and the performance of this dispersion in the coating process was evaluated.

The films plasticized with the sorbitol–glycerol combination showed greater stability during nine months than did films plasticized with either polyol separately. Used together, the different molecular sized polyols appeared to increase the bonding between the constituents. Aqueous-based amylose-rich maize starch dispersion was developed and continuous, transparent and flexible films could be prepared out of the highly amorphous dispersion. The coating process succeeded with this film-forming dispersion without any difficulties. The coating study verified that the dispersion produces smooth coatings at suitable coating temperature and that it is a rapidly releasing potential coating material for pharmaceutical dosage forms. Future work should continue the development work of the dispersion and study the long-term stability of the film-coated tablet.

ABBREVIATIONS

A-RS	amylose-rich starch
EC	ethylcellulose
FT-IR	Fourier transform infrared spectroscopy
FT-NIR	Fourier transform near infrared spectroscopy
HPMC	hydroxypropyl methylcellulosa
HPMCAS	hydroxypropyl methylcellulosa acetate succinate
NMR	nuclear magnetic resonance
R_a	roughness
RH	relative humidity
WVTR	water vapour transmission rate
XRD	X-ray diffraction

LIST OF ORIGINAL PUBLICATIONS

This study is based on the following original articles, which are referred to in the text by their Roman numerals.

I Krogars, K., Heinämäki, J., Karjalainen, M., Niskanen, A., Leskelä, M,. and Yliruusi, J., 2003. Enhanced stability of rubbery amylose-rich maize starch films plasticized with a combination of sorbitol and glycerol. Int. J. Pharm., 251, 205-208.

II Krogars, K., Antikainen, O., Heinämäki, J., Laitinen, N., and Yliruusi, J., 2002. Tablet film-coating with amylose-rich maize starch. Eur. J. Pharm. Sci., 17, 23-30.

III Krogars, K., Heinämäki, J., Karjalainen, M., Rantanen, J., Luukkonen, P., and. Yliruusi, J., 2003. Development and characterization of aqueous amylose-rich maize starch dispersion for film formation. Eur. J. Pharm. Biopharm., 56, 215-221.

IV Krogars, K., Heinämäki, J., Antikainen, O., Karjalainen, M., and Yliruusi, J., 2003. A novel amylose corn-starch dispersion as an aqueous film coating for tablets. Pharm. Dev. Tech., 8, 211-217.

1. INTRODUCTION

Tablets are the most widely used drug form and often they are film-coated for purposes of masking the taste, for recognition, or for controlled release purposes. Cellulose derivatives are the most common pharmaceutical coatings. In the area of food for biobased packaging and edible coating, films made of starch are of great interest because of the biodegradable and safe nature of starch (Kester and Fennema, 1986; Haugaard et al., 2001). The possibility of using amylose for the production of self-supporting films was recognized by Wolff and co-workers fifty years ago (Wolff et al., 1951). The fact that starch and especially amylose-rich starch make strong films with low oxygen permeability (Mark et al., 1966; Forssell et al., 2002) has generated considerable interest in this hydrophilic biopolymer. Starch is also highly cost-effective. These same properties make amylose-rich starch a promising coating material for pharmaceutical purposes. In combination with ethyl cellulose, amylose has been used for colon targeting (Milojevic et al., 1995; Milojevic et 1996a, 1996b; Siew et al., 2000a; 2000b). Palviainen and co-workers (2001) have studied native starch-based coatings for pellets and tablets using a warm solution. Extensive research on starch coating for pharmaceutical purposes has nevertheless not been carried out.

Several studies have reported the aging of rubbery starch films during storage, leading to marked changes in properties (van Soest and Knooren, 1997; Forssell et al., 1999). Aging has been a limiting factor for the use of starch for barrier purposes in food technology.

Water is for safety, ecological and cost reasons the coating medium of choice. Starch is not soluble in water at ambient temperature, however, and in food applications starch films have been made by casting from hot solutions or by thermo-mechanical processing techniques such as extrusion (van Soest et al., 1996) or compression moulding (van Soest and Borger, 1997). In pharmaceutical applications, only ambient tempered solutions or dispersions are currently used. Thus, a dispersion of water-insoluble starch that could be applied at ambient temperature would be desirable for application in pharmaceutical technology.

When materials are to be used in new applications, such as starch for pharmaceutical coatings, it is important to study the effect of excipients and the effect of coating parameters in the coating process. Only in that way can suitable coating

formulations and suitable coating conditions be established. Cast free films give valuable information in material studies. The different preparation techniques for cast films and sprayed films may nevertheless lead to very different properties of the films (Obara and McGinity, 1994). Coating studies are thus essential for the final evaluation of a new coating material and for characterizing suitable coating conditions.

2. REVIEW OF THE LITERATURE

2.1 Native starch

2.1.1 The constituents of starch

Starch is a polymer of glucose units with two main constituents, amylose and amylopectin. Amylose is an essentially linear (alpha 1->4 linked glucose units) (Fig. 1), only slightly branched (Curá et al., 1995). Amylopectin comprises alpha 1->4 linked glucose units interlinked by 1->6 alpha D-glucosidic linkages to form a multiply branched structure (Manners, 1989) (Fig. 1). The ratio of amylose to amylopectin varies with the origin of the starch. Starch granules usually have an amylose content of 16–28%, whereas waxy starches consist solely of amylopectin (Swinkels, 1985). High amylose starches (amylomaize, rice, wrinkled pea) have an amylose content of over 50%.

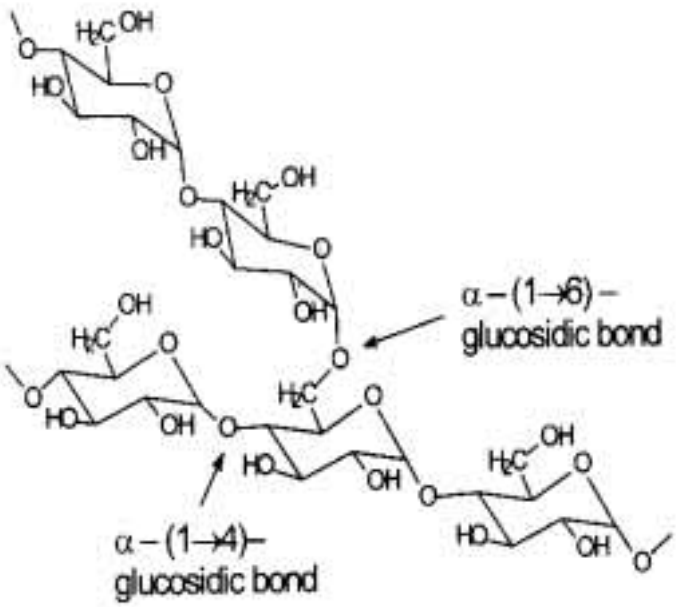

Figure 1. The two different linkages between the glucose monomers in starch (Friedman et al., 1999, with permission).

2.1.2 Polymorphism of starch

The three main crystalline allomorphs of starch are A, B and V. The A-type occurs essentially in cereals and the B-type in tubers. In starch films, B-type crystallinity is rapidly formed in amylose-rich materials and slowly during the aging of amylopectin-rich materials (van Soest and Essers, 1997) (see section 2.2.1, Factors affecting starch films). The A-type starch has 12 glucose residues per unit cell located in two left handed, parallel-stranded double helices (Imberty et al., 1988) (Fig. 2). The helices are packed in a parallel fashion and four water molecules can be accommodated in one unit cell. The double helices are crystallized in a face-centred monoclinic space group, where the fibre axis is parallel to the helix axis. The B-type starch also contains two left-handed parallel-stranded double helices (Imberty and Perez, 1988) (Fig. 2); however, in this polymorph form the helices are crystallized in a hexagonal space group (Wu and Sarko, 1978). The channel formed by the hexagons of double helices contains about 36 water molecules per three glucose unit rise in the B-type crystalline structure.

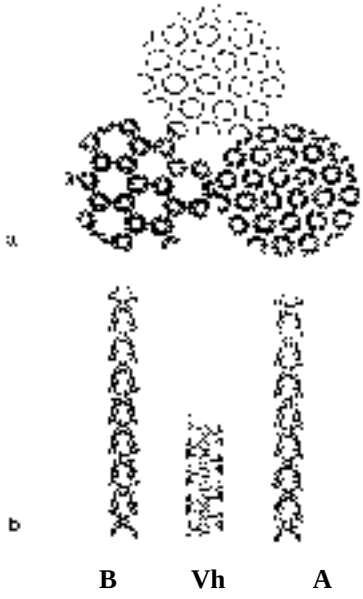

Figure 2. The structure of starch polymorphs of B-type (left), Vh-type (middle) and A-type (right). (a) Projection of the structures on to the plane, (b) drawing of the helices (Gernat et al., 1993, with permission).

An inclusion complex of lipids with amylose (V-type structure) is found in native maize, rice and oat starches (Morrison et al., 1993). The V-type structure is obtained artefactually when single helices of amylose are co-crystallized with other compounds, such as iodine, fatty acids (Takeo et al., 1973; Godet et al., 1993), dimethyl sulfoxide (French and Zobel, 1967), lactones (Heinemann et al., 2001), acetone (Buléon et al., 1990) or alcohols. Starch–alcohol inclusion complexes can be obtained with alcohols such as n-butanol (Hinkle and Zobel, 1968), methanol, isopropanol (Buléon et al., 1990), 1-propanol, 1-penthanol (Polaczek et al., 1999) and ethanol (Le Bail et al., 1995). The Vh-type (hydrated V form) is crystallized in an orthorhombic unit cell with a left-handed, six residue helix (Rappenecker and Zugenmaier, 1981) (Fig. 2).

2.1.3 Structural changes during heating and cooling

When starch is heated in aqueous conditions**,** the starch granules begin to swell and the molecular order within the starch granule collapses. Irreversible changes occur, such as crystallite melting, viscosity development and solubilization. This phenomenon, which is called *gelatinization* (Atwell et al., 1988), takes place at about 55-80°C depending on the type of starch (Swinkels, 1985). The term gelatinization has sometimes been used as a synonym for pasting (Atwell et al., 1988). However, *pasting* is better defined as the phenomenon following gelatinization in the dissolution of starch, leading eventually to total disruption of the granules (Atwell et al., 1988), which occurs at temperatures of about 100-160°C (Swinkels, 1985). Yet a third definition of pasting is that pasting is the sequence of events that starch undergoes when both heated and stirred to apparent “solubilization” (Atwell et al., 1988). The solution formed is called a *starch paste*. Upon cooling, the starch begins to undergo *retrogradation*, which means that the starch molecules begin to reassociate in an ordered structure (Atwell et al., 1988). First two or more molecules may form a simple juncture point, and the juncture points may then develop into ordered regions. Finally, a crystalline order may appear and the chains convert into an insoluble form. Starch retrogradation can be studied by rheological methods, X-ray diffraction, thermal analysis and spectroscopic methods (Abd Karim et al., 2000). When cooked starch pastes are cooled retrogradation takes place and this is manifested by the formation of a precipitate or a

gel (Swinkels, 1985). As dilute (<1.5%) amylose solutions are cooled, the amylose precipitates out, forming a gel of increasing modulus with increasing concentration (Ellis and Ring, 1985). The chain length of amylose affects the phase behaviour as follows: chain lengths of < 110 residues form precipitates, those of 250-660 residues form both precipitate and gel, and gelation predominates for longer chain lengths (>1100) (Gidley and Bulpin, 1989). The critical concentration for gelation (approx. 1%) is nearly independent of chain length, however (Gidley, 1989). The amylose concentration affects the properties of the formed gels. Amylose-rich gels exhibit higher mechanical and thermal resistance and they degrade less both chemically and enzymatically as compared with amylopectin-rich gels (Leloup et al., 1991). The shape of aggregates formed out of a steam jet cooked solution upon cooling has been investigated by Fanta and co-workers (2002). When normal maize starch, high amylose maize starch and rice starch were cooled, two different kinds of particles were formed. The small particles were disc or torus in shape, while the larger particles were almost spherical.

2.2 Starch as a film former

2.2.1 Factors affecting starch films

The crystal type is different for amylose-rich starch films depending on the drying temperature (Bader and Göriz, 1994a). When a lower drying temperature is used, a B-type pattern is formed, whereas at temperatures above 80ºC a film with A-type pattern is obtained. Drying temperature also affects the degree of crystallinity; films formed at room temperature (20ºC) obtain a higher crystallinity than films formed at elevated temperature (68ºC) (Rindlav et al., 1997). An increase in air humidity increases the crystallinity of both starch films (Rindlav et al., 1997) and amylopectin films, but air humidity has no effect on the crystallinity of amylose films (Rindlav-Westling et al., 1998; Stading et al., 2001). For compression-moulded starch films, it was shown that both the properties of the potato starch and the applied processing conditions affected the amount of B-type crystallinity (Hulleman et al., 1999).

In addition to the environmental factors affecting starch film formation, also the amylose/amylopectin ratio and co-materials, such as plasticizers, affect it. For unplasticized films an increase in amylose content leads to a decrease in carbon dioxide and water vapour permeabilities (García et al., 1999) and an increase in both

tensile strength and elongation (Lourdin et al., 1995). For plasticized (glycerol) films, however, the tensile strength increases with amylose content while the elongation decreases. The tensile strength and the elongation reach a plateau, however, and the mechanical properties stay unchanged above an amylose content of about 30–40%. The amylose/amylopectin ratio also affects the morphology of the formed films: higher amylose content leads to a more homogeneous film, and higher amylopectin content increases phase separation (Rindlav-Westling et al., 2002).

Plasticizers are added to polymers to increase the ductility of the material. Glycerol, sorbitol, fructose, glucose, sucrose, xylose, lactic acid sodium, urea, diethylene glycol, polyethylene glycol (PEG 200), and glycerol diacetate are materials used as plasticizers in starch films (Kalichevsky et al., 1993; Arvanitoyannis et al., 1994; Lourdin et al., 1997b; Rindlav-Westling et al., 1998; Gaudin et al., 1999). The first two excipients are the most widely studied (Fig. 3). At low plasticizer contents the plasticizer (glycerol or sorbitol) does not have the classical effect of elongating starch films (Lourdin et al., 1997a; Gaudin et al., 1999). This phenomenon, well known from synthetic polymer science, is called the antiplasticization effect. The elongation starts to increase, with higher plasticizer contents than approximately 15% for glycerol and 27% for sorbitol. The tensile strength of starch films decreases continuously with the increasing plasticizer content.

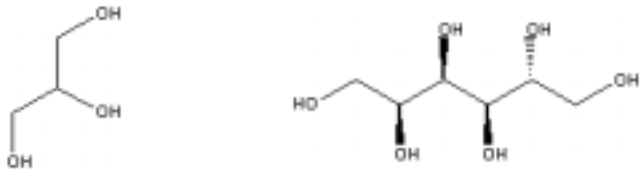

Figure 3. Structures of glycerol (left) and sorbitol.

2.2.2 Properties of starch films

Films formed of starch are amorphous, the degree of crystallinity varying with the film forming conditions. The mechanical and barrier properties of starch films depend (among other things) on the environment and place limitations on the use of the films.

The mechanical properties of pure amylose and pure amylopectin films are different, amylopectin films having a more brittle character than amylose (Myllärinen et al., 2002b). Table 1 shows the mechanical properties of pure amylose and pure amylopectin films compared with film-formers currently used as coating materials in pharmaceutical applications. Amylose films have a tensile strength equal to or stronger than the other coating polymers. Amylopectin films are clearly weaker (i.e. lower tensile strength) than the amylose films. The amylose and amylopectin films have higher elongation values than the polymers they are compared with, except for Eudragit® E. The reported elongation value for this polymer is 13 to 50 times higher than that for amylose/amylopectin films.

Table 1. Mechanical properties of films made of some film-forming polymers.

Polymer	Elongation (%)	Stress at break (MPa)	Plasticizer	Reference
Amylose	31	20	40% glycerol	Rindlav-Westling et al., 1998
Amylopectin	29	6	40% glycerol	Rindlav-Westling et al., 1998
HPMC	4-14	-	3% propylene glycol	Nagarsenker and Hegde, 1999
Eudragit® E	400-1500	-	15% triacetin + different secondary plasticizers	Lin et al., 1991
Eudragit® L	1-3	14-25	20% triethyl citrate	Obara and McGinity, 1995
HPMC AS	1-3	5-16	28% triethyl citrate	Obara and McGinity, 1995
EC	1-7	-	25-35% of different plasticizers	Hutchings et al., 1994

HPMC, hydroxypropyl methylcellulose; Eudragit® E and L, methacrylic acid copolymers; HPMC AS, hydroxypropyl methylcellulose acetate succinate; EC, ethyl cellulose.

The oxygen permeability of native starch films is low. Plasticizer content and the surrounding air humidity have an effect: higher plasticizer content and/or a higher air humidity lead to increasing oxygen permeability (Arvanitoyannis et al., 1996), whereas a higher crystallinity leads to a reduction in gas (O_2, N_2, and CO_2) and water vapour permeabilities (Arvanitoyannis et al., 1994; Arvanitoyannis et al., 1996).

Pure amylose films are stable in water; only 3% were dispersed during three hours (Myllärinen et al., 2002a). About 60% of pure amylopectin films dispersed into the water during the same time.

Amorphous starch films are in nonequilibrium state, characterized by molecular disorder. They may be either in *glassy state* or in *rubbery state*. The glassy state, when the material is hard and brittle, is formed by sufficiently rapid evaporation of the solvent or by rapid cooling. With an increase in temperature, glassy material may transform into the less viscous rubbery state. The state transition from glassy to rubbery is called the glass transition and it occurs over a specific temperature range. A significant decrease in stiffness and increase in molecular mobility take place at the glass transition temperature (Roos, 1995). The glass transition temperature of films depends on factors such as the particular polymer employed, plasticizer added (Lourdin et al., 1997b), and the amount of plasticizer (Kalichevsky et al., 1993). Water acts as a plasticizer for starch films (Forssell et al., 1996). Increasing the plasticizer content in films leads to a lower glass transition temperature. At high (50% of polymer weight) plasticizer (fructose) content the transition was broadened, which suggested a multiphase system containing amylopectin-rich and fructose-rich regions (Kalichevsky, et al., 1993). Lourdin and co-workers (1997b) showed that phase separation occurred for starch films containing more than about 13% of lactic acid sodium. A similar phase separation was not seen for glycerol and sorbitol, but the authors speculated that it would occur at higher plasticizer contents. Forssell and co-workers (1997) observed phase separation for glycerol at intermediate (29%) glycerol and water contents (Forssell et al., 1997).

2.2.3 Stability of starch films

Several studies have reported changes in the mechanical properties of rubbery starch films during storage (Van Soest and Knooren, 1997; Forssell et al., 1999). The elongation of films decreases while the tensile strength increases. The changes occurring during storage have been explained by changes in water content, glass transition temperature (Shogren, 1992) and crystallinity (van Soest and Knooren, 1997). From calorimetric and X-ray diffraction studies, Forssell and co-workers (1999) concluded that the major change in the mechanical properties of starch films is due to the reorientation and/or crystallization of amylose and amylopectin molecules. Kuutti and co-workers (1998) concluded from atomic force microscope (AFM) friction measurements that the small molecular plasticizer, i.e. glycerol, was migrating to the surface during aging. Recently somewhat different results have been reported; amylose

films (plasticized with 0, 10 or 30% of glycerol) showed a B-type diffraction pattern, and no changes in crystallinity were observed during two months storage (relative humidity [RH] 0, 54 and 91% at room temperature). For most amorphous amylopectin films, no change occurred during the storage period. However, for amylopectin films with 30% of glycerol stored at RH 91%, the crystallinity increased from 10 to 19% within one month. The increasing crystallinity was attributed to the rubbery state of the highly plasticized amylopectin films (Myllärinen et al., 2002a). Extruded starch rods in the glassy state have also shown a progressive embrittlement on aging (Lourdin et al., 2002).

2.3 Film-coating

2.3.1 Films from polymer dispersions

The paint, paper and textile industries have been using latexes for film formation for decades, but the pharmaceutical industry began to use them in substantial amounts in coating only in the 1980s and 1990s. Latexes can be described as colloidal polymer particles dispersed in a liquid and are prepared by emulsion polymerization. Theories proposed for the film formation of latexes and more generally for polymer dispersions are reviewed in the following. Dillon et al. (1951) described how the bonding of two or more dry polymer particles "takes place by the viscous flow of the polymer, the surface tension of the plastic furnishing the necessary shearing stress" (Fig. 4).

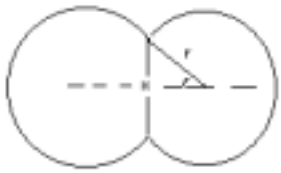

Figure 4. The coalescence of particles by fusion due to viscous flow (modified from Dillon et al., 1951).

Brown (1956), however, suggested that for non-dry particles film formation will occur if the capillary pressure is greater than the resistance of the

polymer particles to deformation (Fig. 5). The film formation will be affected by the surface tension, particle size of the dispersion, drying process time, temperature and the rheological properties of the polymer.

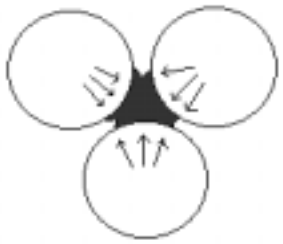

Figure 5. Capillary water acting as a contracting force (modified from Brown, 1956).

The influence of "autohesion" was discussed by Voyutski (1958). Autohesion is the term he uses to describe the diffusion of chain polymer molecules from one particle to another, forming the strong stable links. Autohesion is proposed necessary to obtain a stable film. Film formation was described as occurring in three different stages. Evaporation of water occurs in the first stage, and, as a consequence, the concentration increases. In the second stage the water continues to evaporate and, as a consequence of capillary forces, the polymer particles move closer to each other and the deforming of particles takes place. Autohesion takes place in the third stage. During the last decade a model combining earlier theories has been presented where (1) capillary forces and (2) interfacial forces are the two factors proposed to promote the film coalescence (Eckersley and Rudin, 1990). It was experimentally shown that the minimum film-forming temperature is higher for particles of larger size and that the degree of film fusion is a function of particle radius—small particles fuse more completely at room temperature. It was also experimentally shown that the minimum film-forming temperature is higher for polymers of greater rigidity (Eckersley and Rudin, 1994). For hydroxypropyl methylcellulose acetate succinate (HPMC AS), a pseudolatex used in pharmaceutical technology, Nagai and co-workers (1997) suggest the following theory for film formation. "The plasticizer is separated from water phase during drying process and it dissolves or gelates the particles of HPMC AS. The particles then fuse to form a film".

2.3.2 Coating liquid and substrate considerations

The properties of the coating liquid affect the resulting film coating. For coating solution containing hydroxypropyl methylcellulose, the low molecular weight grades showed the highest film-coating roughness and an increase in molecular weight caused a decrease in surface roughness, which was at a minimum with intermediate molecular weight grades (Rowe, 1978). Increased viscosity of the coating liquid also caused an increase in roughness (Rowe, 1978) because higher viscosity leads to higher contact angles (Twitchell et al., 1995). With increasing viscosity the momentum that needs to be provided to accomplish a smooth film increases.

The substrates (tablets, granules, pellets etc.) used for coating should possess properties such as sufficient tumbling resistance and endurance to high temperatures. Substrate hydrophobicity influences negatively on film adhesion when the polymer is plasticized with hydrophilic compounds. However, when water-insoluble plasticizers are used, the hydrophobicity of the tablet does not affect adhesion (Felton and McGinity, 1997). It has also been shown that increasing the amount of hydrophobic agent in the substrate decreases the adhesion between substrate and aqueous-based coating (Felton and McGinity, 1996). The adhesion of the polymer to the substrate increases with the roughness of the substrate (Felton and McGinity, 1996).

2.3.3 Coating process considerations

The conditions of the coating process have a significant effect on the resulting film coating. Film defects appear if the conditions are not optimal. Some application conditions influencing the coating are shown in Figure 6. The optimum coating temperature varies with the polymer. Heinämäki et al. (1997) found for an aqueous solution of hydroxypropyl methylcellulose (HPMC) an increase in film thickness with increasing inlet air temperature and an increase in moisture content of the film with decreasing coating temperature. On crushing strength and disintegration time the effect of coating temperature was not significant. Reiland and Eber (1986) reported an increase in surface roughness with inlet air temperature (HPMC). The inlet air temperature can also influence the drug release rate. A higher inlet temperature leads

to lower rate of drug release when the coating is done with ethyl cellulose (Parikh et al., 1993).

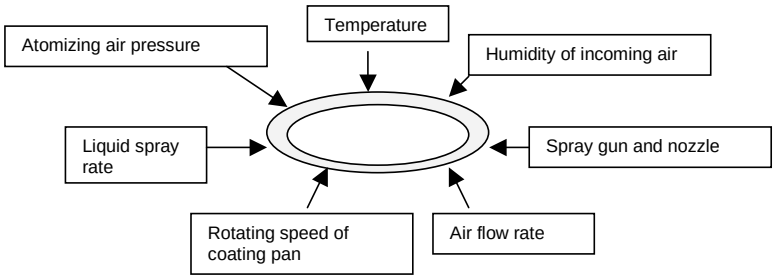

Figure 6. Some coating conditions influencing the resulting film.

A study with a low-viscosity HPMC solution showed no influence of atomizing air pressure on roughness (Reiland and Eber, 1986), whereas for an aqueous HPMC solution of higher concentration an increase in atomizing air pressure led to reduced surface roughness. An increase in liquid spray rate decreases the exhaust air temperature (Rowe and Forse, 1982) and increases droplet size (Aulton and Twitchell, 1995). This in turn can have secondary effects on tablet film coating. The effect of liquid spray rate on film quality is not clear, however. A higher rotation speed of the coating pan leads to film-coated tablets (HPMC) with better physical appearance (Heinämäki et al., 1997). The influence of rotation speed is, however, related to the liquid spray rate. The air flow rate has only a minor effect on surface roughness; a reduction in air flow rate seems to produce smoother films (Aulton and Twitchell, 1995). An increase in humidity of incoming air influenced negatively on appearance: as it resulted in a clearly rougher and more unhomogeneous coating surface than with lower inlet air humidity (Ruotsalainen, 2003). The result was explained by the decrease in magnitude of drying (i.e. water evaporation), due to the higher humidity, which slowed the coalescence of the coating polymer (HPMC).

3. AIMS OF THE STUDY

Although starch is a well-known excipient in pharmaceutical technology, it has not been used for coating purposes. The aim of this study was to explore the possibility of using starch, and specifically amylose-rich maize starch, for aqueous-based tablet coating. Aging and nonuser-friendly hot coating solutions are problems associated with starch and these limitations were of interest in the study. The specific objectives of the work were

For aqueous amylose-rich maize starch heated solution

1. to study the stability of free amylose-rich starch films plasticized with sorbitol and glycerol separately and in combination,
2. to optimize the plasticizer content and the coating process conditions.

For aqueous amylose-rich maize starch dispersion

3. to develop a film-forming coating dispersion,
4. to study the behaviour of the dispersion in the coating process.

4. EXPERIMENTAL

4.1 Materials

Amylose-rich maize starch (Hylon VII, National Starch, Germany) with amylose content 70% and amylopectin content 30% was used for the preparation of free films and for coating. The plasticizers sorbitol (Ph. Eur.) and glycerol (85%) (Ph.Eur.) were used as received. Purified water was used as a solvent.

4.2 Preparation of heated solution

The amylose-rich starch solution was prepared in a high-pressure reactor. The suspension was heated, with continuous stirring (100 rpm), to 160 ± 1°C (pressure 4 bar), after which the solution was cooled to 95 ± 2°C and removed from the reactor (I, II).

4.3 Preparation of dispersion

Amylose-rich maize starch (2% w/w) and purified water were stirred (100 rpm) and heated to 160°C in a pressure reactor (pressure 4 bar). The chamber was cooled to 95°C and the still hot solution was cooled in an ice bath to a temperature of 10, 40 or 80°C (Fig.7). When the target temperature was reached, ethanol (1:1) was added with continuous blending. The dispersions that formed are referred to as *"dispersion 10"*, *"dispersion 40"* and *"dispersion 80"* according to the temperature of preparation (III). The dispersions were mixed with a magnetic stirrer for 1 h after the ethanol addition. Twenty-four hours after preparation the dispersions were analysed, with all measurements made in triplicate.

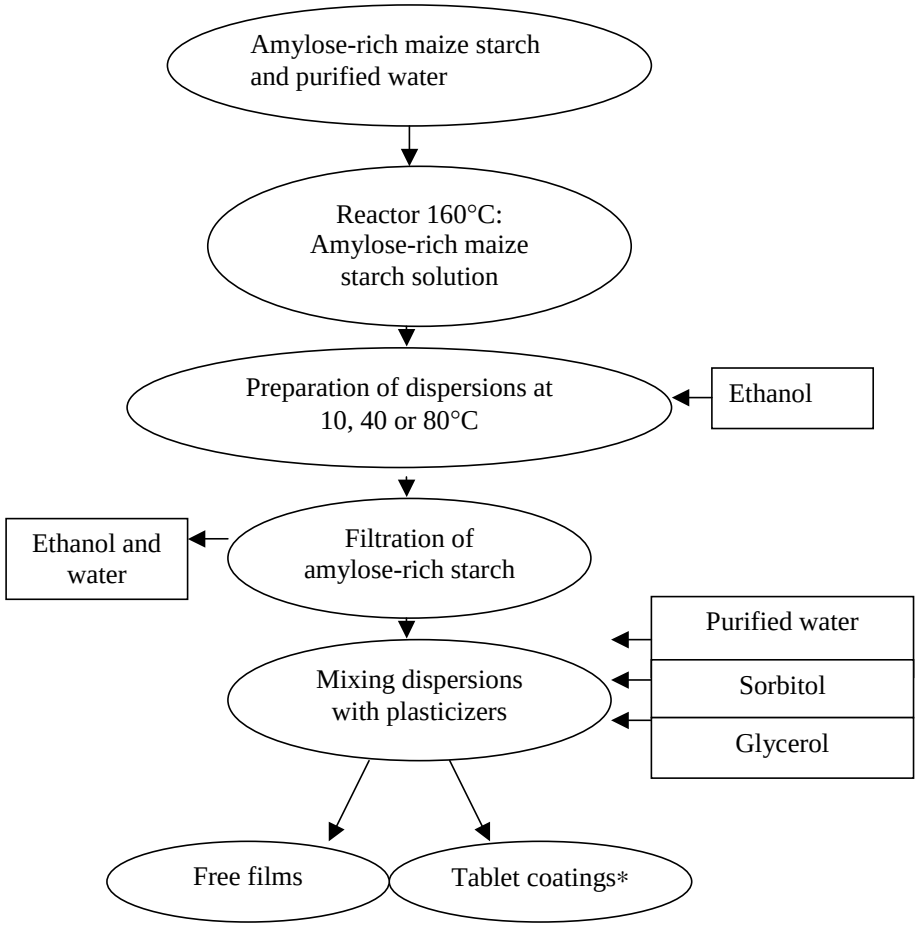

Figure 7. Preparation of amylose-rich starch dispersion. (*with the dispersion prepared at 40°C).

The amylose starch dispersion for coating was prepared as follows (IV): the heated solution (160ºC) was kept in an ice-bath until a temperature of 40 ± 2°C was reached, then ethanol was added with continuous blending. The dispersion that formed upon ethanol addition was blended for 2 h. The water/ethanol mixture was removed by filtration the next day.

4.4 Evaluation of dispersions

4.4.1 X-ray diffraction (XRD)

The dispersions (III, IV) were studied with use of an X-ray diffraction (XRD) theta-theta diffractometer (Bruker AXS D8, Germany). The experiments were performed in symmetrical reflection mode with CuK_α radiation (1.54 Å) using Göbel Mirror bent gradient multilayer optics. The scattered intensities were measured with a scintillation counter. The angular range was from 2^o to 40^o, in steps of 0.05^o, and the measuring time was 10 s/step. The instrumental broadening was estimated as 0.03^o, from a reflection of silicon.

4.4.2 FT-NIR

The near-infrared spectra of dispersions (III), were measured with a Fourier Transform (FT-NIR) spectrometer (Bomem MD-160 DX, Hartmann & Braun, Quebec, Canada) using Bomem-GRAMS software (v. 4.04, Galactic Industries Inc., Salem, NH, USA) and Teflon as a reference (99% reflective Spectralon, Labsphere Inc., North Sutton, NH, USA). The spectra were recorded over a range of 10000-4000 cm^{-1} with a resolution of 8 cm^{-1}; an average of 40 scans were used.

4.5 Preparation of free films

4.5.1 Solution-based films (I)

The amylose-rich starch content of the solution was 5% and the plasticizer content varied (50%, 100%, 120% of the polymer weight). Plasticizers glycerol and sorbitol (1:1) were mixed with the solution and films were prepared immediately. The solution was poured into Teflon moulds, which were kept in an oven for approximately 2 h at 70°C until edge curling occurred and the films were dry. Films were kept for 2 days at 25°C (60% RH) (initial) and then stored for 9 months under conditions of 25°C (60% RH) and 40°C (75% RH) before analysis.

4.5.2 Dispersion-based films (III)

The day following the preparation (section 4.3), the dispersions were filtered and purified water and plasticizers (glycerol and sorbitol) were added. The amylose-rich starch content of the dispersion was 5%. The glycerol and sorbitol concentrations were both 50% of the polymer content (total 100%). The plasticizers were blended with the suspension for 2 h before casting of films. The suspension was poured onto Teflon plates and transferred to an oven at 70°C and 17% RH (2 h). The films were stored in a controlled atmosphere, at 25°C and 60% RH, for 1 week before testing. All measurements were done in triplicate.

4.6 Evaluation of free films

4.6.1 X-ray diffraction (XRD) and FT-NIR

The free films prepared from solution were analysed by X-ray diffraction with a Bruker AXS (Germany) (I). Measurements were performed in symmetrical reflection mode with CuK_{α} radiation. The angular range was from 2^{o} to 60^{o} (at 2θ) with steps of 0.02^{o} and the measuring time was 20 s/step in all measurements. The XRD and FT-NIR evaluation of the free films prepared from dispersions (III) were analysed as described in the sections 4.4.1 and 4.4.2 respectively.

4.6.2 Mechanical properties

The mechanical and stress–strain properties of free films (I, III) were determined using a material testing machine (Lloyd LRX, Lloyd Instruments Ltd., Great Britain). The films were cut into strips and mounted on the machine. In the initial position the grips were 40 mm apart. The extension speed was 10 mm/min. Stress–strain curves were recorded, and the tensile strength (load at break/initial cross-sectional area) and elongation (%) at break were measured. For the calculation of cross-sectional area the thickness was measured with a micrometer at three points.

4.6.3 Permeability properties

For measurements of water vapour transmission rate (WVTR), the free films (I) were cut to a suitable size and fixed onto glass bottles with calcium chloride ($CaCl_2$) and immediately sealed with metal rings. The bottles were held at 20°C and 60% RH and were weighed several times during 28 h. Each measurement was performed in triplicate. The WVTR was calculated as follows: $P = (W \times L)/(A \times T \times \Delta p)$, where P is the permeability constant, W is the weight of water diffusing through a film of thickness L and area A, T is the time in hours during which water diffuses, and Δp is the vapour pressure difference across the film at 1 atm. The water vapour pressure in the bottle was assumed to be zero.

4.7 Film coating of tablets

4.7.1 Coating equipment

A side-vented pan-coating apparatus (Thai coater, model 15, Pharmaceuticals and Medical Supply Ltd Partnership, Thailand) was used for coating, in both the solution-based and dispersion-based studies (II, IV). This pilot-scale coating apparatus was instrumented, making it possible to control several coating parameters (Table 2) and to record the coating parameters during the coating process.

Table 2. Parameters controlled during the coating process.

Parameter	Unit
Temperature in coating pan	°C
Outlet temperature	°C
Inlet temperature	°C
Atomizing air pressure	kPa
Spray rate of coating solution	g/min
Rotating speed of pan	rpm
Air flow	l/s
Pan pressure	Pa

4.7.2 Solution-based coatings (II)

The prepared solution, with the amylose-rich starch content of 4%, was kept at 80 ± 2°C to avoid precipitation. A central composite face (CCF)-centred experimental design was used. Three independent variables were studied: the concentration of the plasticizer mixture (1:1) (X_1), the temperature of the coating pan (X_2) and the spray rate of the coating solution (X_3) (Table 3). Nine hundred grams of theophylline tablets were coated in each batch. The composition of the double concave core tablets was as follows: theophylline anhydrate 5%, lactose 30%, microcrystalline cellulose 56%, talc 8% and magnesium stearate 1%. The coating process was started when the temperature of the coating pan reached the desired temperature. The atomizing air pressure was 300 kPa**,** the air flow rate 20 l/s, the pan pressure –5 Pa, and the rotating speed of the pan was 7 rpm. The tablets were kept at room temperature (21 ± 2°C) for at least 24 h before they were studied.

Table 3. Levels of independent variables in the solution coating study.

	Level		
Independent variable	-1	0	+1
X_1, Plasticizer concentration (% of polymer)	33	66	100
X_2, Temperature of coating pan (°C)	40	55	70
X_3, Spray rate of coating solution (g/min)	4.5	9	13.5

4.7.3 Dispersion-based coatings (IV)

Purified water was added to the dispersion in the desired amount and the plasticizers were added. The coating dispersion consisted of 5% amylose-rich starch prepared at 40°C. The sorbitol and glycerol (1:1) content was 66% of the polymer weight. The steps of preparation for the coating dispersion are shown in Figure 7.

The coating conditions were as follows: pan pressure -5 Pa, air flow rate 20 l/s, pan speed 7 rpm and spray rate of coating dispersion 8 g/min. Theophylline (20 mg) tablets, in batches of 900 g, were coated. The temperature of the coating pan and the atomizing air pressure were independent variables (Table 4). A 3^2 experimental design was used. The experimental design consisted of nine experimental points and in

addition the centre point was carried out in triplicate so that the total number of experiments was 11.

Table 4. Levels of independent variables in the dispersion based study.

	Level		
Independent variable	-1	0	+1
X_1, Temperature of coating pan (°C)	30	50	70
X_2, Atomizing air pressure (kPa)	150	300	450

4.8 Evaluation of film-coated tablets

4.8.1 Roughness

The roughness of the coated tablets was measured by a novel optical method (II and IV) and by laser profilometry (II). Laitinen and co-workers (2002) have described the principle of the optical analysis method. The optical instrument consists of the imaging unit, which has a light source and a charged-coupled device (CCD) camera (JAI, CV-M50, Copenhagen, Denmark) with lens objective, which is connected to a frame grabber (WinTV, Hauppage Computer Works Inc., Hauppage, NY, USA) and a PC. The components of the illumination system include a lamp housing (Model 60000, Series Q Housing, Oriel Instruments, Stratford, CT, USA), a 100-W quartz tungsten halogen lamp, and a collimating lens assembly (Oriel Instruments, Stratford, CT, USA). The light source is connected to a stabilized DC power supply (model 68735, Oriel Instruments, CT, USA). The principal idea is that smooth surfaces have small variations in grey-scale values, and the rougher the surfaces are, the larger are the grey-scale value variations. As the sample is illuminated from only one side, the other side of the surface becomes somewhat darker, which results in increasing grey-scale values. This effect was first corrected by levelling the curve. The roughness parameter was then calculated for each curve using Equation 1. Roughness is the arithmetic average of the absolute values of all points (pixels) of the profile.

$$Roughness = \frac{1}{800} \times \sum_{i=1}^{800} |y_i - \bar{y}| \quad (1)$$

where y_i is the measured i^{th} grey-scale value and $\bar{y}$ is the average of all the points in the roughness profile.

The non-contacting laser profilometry (II) (UBM Microfocus Measurment System, UBM Mebtechnik GMbH, Ettlingen, Germany) measurements were conducted by scanning three parallel 4 mm lines with 1 mm between the lines of four tablets. The roughness parameter, Ra, was calculated from the data of 1000 pixels/cm (x-y resolution) and z resolution of 0.1 μm.

4.8.2 Drug release and crushing strength

Other responses evaluated for film-coated tablets were weight (n=20) and radial crushing strength (n=20) (Erweka Multicheck, Erweka GmbH, Germany) (II, IV). Drug release was studied using a paddle method where the dissolution medium was 900 ml of 0.1 N hydrochloric acid at 37°C ± 0.5 (Sotax AT6, Sotax AG, Switzerland) (II, IV).

4.8.3 Statistical analysis

The effects of the variables were modelled using a second-order polynomial equation. The modelling was done in the same manner for the solution-based (II) and dispersion-based coatings (IV). The model was simplified with a multi-linear backwards, step-wise regression technique. The least significant terms were excluded from the model as long as the predictive power (Q^2) of the model was increasing. The modelling was performed using Modde for Windows (Version 4.0, Umetri AB, Sweden).

5. RESULTS AND DISCUSSION

5.1 Plasticization of amylose starch films

5.1.1 Enhanced stability with plasticizer combination

The films plasticized with either of the plasticizer (glycerol or sorbitol) had suffered from marked changes in visual appearance during nine months (Table 5). The films plasticized with the sorbitol–glycerol combination were stable in respect of visual appearance (Fig. 8), crystallinity (Fig. 9), elasticity and water vapour permeability. These films were chosen for further studies. These films had a partly B-type crystalline structure (Fig. 9). In earlier work where starch films were plasticized with just one plasticizer (glycerol), the mechanical properties of the films changed during storage (van Soest and Knooren, 1997). Van Soest and Essers (1997) showed, however, that the changes in the mechanical properties were less pronounced for amylose-rich starch sheets. Migration of plasticizing glycerol to the surface has also been noticed (Kuutti et al., 1998; Forssell et al., 1999). Roman and Fulper (2000) studied the migration of polyol plasticizers in soft gelatin capsules and found that all their polyols (i.e. glycerol, sorbitol, sorbitan and mannitol) migrated from the gelatin capsule shells into the fill material.

Table 5. Appearance of amylose-rich maize starch films stored for 9 months at 25°C and 60% RH.

	Total plasticizer content*		
Plasticizer(s)	50%	100%	120%
Glycerol	Hard and wavy	Glycerol droplets on film surface	-
Sorbitol	Sorbitol crystals on film surface	Sorbitol crystals on film surface	-
Glycerol:Sorbitol (1:1)	Hard and wavy	Appearance as the initial film	Opal and tacky film

* w/w on the basis of Hylon VII content.

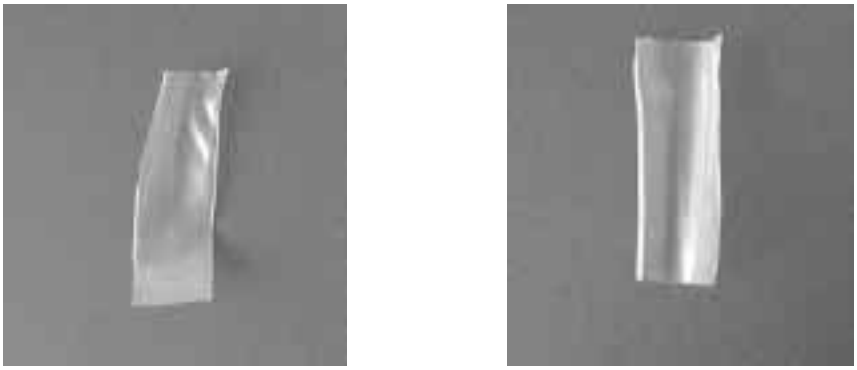

Figure 8. Micrographs of free films prepared from solution plasticized with the sorbitol–glycerol combination, initial (left) and after 9 months.

The combination of plasticizers in the present study seems to enhance the stability of free amylose starch films. Possibly the plasticizers, being of different size organize in such a way that more hydrogen bondings are generated and migration of the polyols is thereby hindered. Possibly, too, the hydrogen bondings hinder the ability of the starch polymer to move and in that way prevent further crystallization of starch. A study by Westhoff and co-workers (1979) in which films were prepared from a mixture of starch and polyvinyl alcohol plasticized with combinations of polyols supports the results of our study. For this polymer blend, the combination of sorbitol and glycerol (3:1) likewise improved the stability of the mechanical properties.

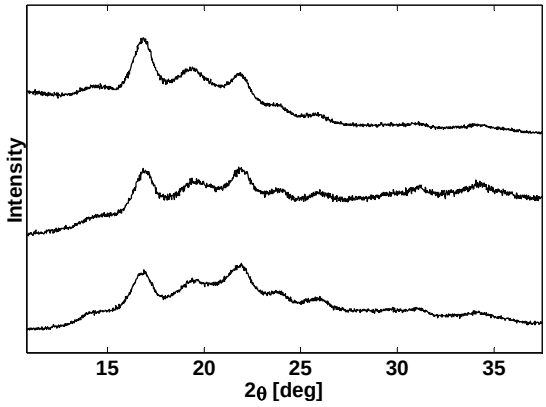

Figure 9. XRD intensity curves for amylose-rich starch films prepared from solution, and plasticized with the sorbitol–glycerol combination. Films stored for 9 months at 40°C, 75% RH (top curve), at 25°C, 60% RH (middle curve) and the bottom curve was recorded from the fresh film.

5.1.2 Amount of plasticizer

Based on preliminary studies the plasticizer content chosen for the study of free amylose-rich starch films was higher than the amounts of plasticizer generally used for starch. The amount of plasticizer in conventional pharmaceutical coating materials is also usually lower, i.e. between 0 and 35% w/w expressed as weight percentage of the polymer. Some examples of amounts of plasticizer studied are the following: for hydroxypropyl methylcellulose 0-20% (Johnson et al., 1991) and 10-30% (Aulton et al., 1981; Heinämäki et al., 1994) and for ethyl cellulose pseudolatex 25-35% (Hutchings et al., 1994). Exceptionally for cellulose acetate pseudolatex films plasticizer concentrations as high as 90-150% have been studied (Sastry et al., 1998).

Starch requires a plasticizer content of roughly 20% to avoid the antiplasticization effect (Lourdin et al., 1997a). However, plasticizer content and water content influenced, among other things, the mechanical properties of free films (van Soest and Knooren, 1997). The strength of the films (and coatings) decreases as the amount of plasticizer increases. The oxygen permeability is almost independent of the amount of plasticizer, but increases markedly with water content (Forssell et al., 2002). Plasticizers are usually needed to modify the film properties in order to increase elasticity. Since increasing plasticizer content decreases the strength of films, there are some limitations on plasticizer content. In view of this, it must be emphasized that the plasticizer content used in this study (I) is not suitable for all purposes.

The plasticizer content suitable for coating (II) was less than that for cast free films (I), 66 and 100%, respectively. Indeed studies have shown that there are differences between cast and sprayed films (Obara and McGinity, 1994). When a coating solution or dispersion is sprayed some drying of the droplets will occur on the way from the spray gun to the tablet surface. Moreover, the droplets will hit the surface with force due to the spraying velocity. These circumstances will most likely be of importance in the film formation sequence, and thereby influence such composition aspects as the amount of plasticizer required.

5.2 Amylose starch dispersion

5.2.1 Film formation from dispersions

The free films prepared from the dispersions 10, 40 and 80 differed in physical appearance. The films formed from dispersions 80 and 10 were discontinuous, whereas the film formed from dispersion 40 was transparent, flexible and continuous (Fig. 10). The X-ray diffraction patterns of the films resembled that of B-type starch (Fig. 11). The diffraction peaks characteristic for B-type starches are at 2θ Bragg angles 5.6, 15, 17, 22, and 24 (Le Bail et al., 1993). The reflections at 15° and 17° (2θ) in our films had been shifted to higher 2θ-values, however, which means that distances between the Bragg planes are shorter in our films. From the diffraction patterns it can also be seen that the Vh-type allomorph of dispersion 80 evolved during film formation (and equilibration) into the B-type starch, although the Vh-type pattern could still be distinguished.

Figure 10. Micrograph of a film prepared of dispersion 40.

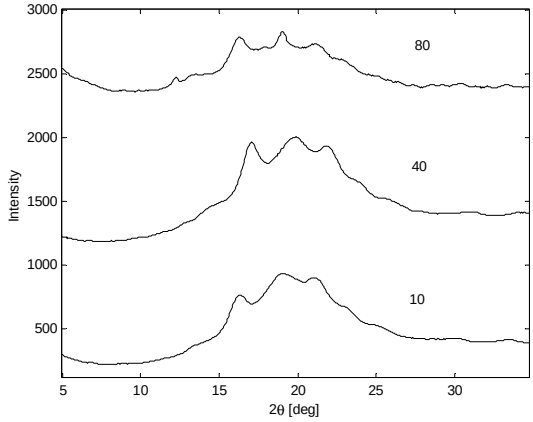

Figure 11. X-ray diffraction patterns of films cast from dispersions prepared at different temperatures.

5.2.2 Effect of temperature on dispersions and films

Amylose-rich starch dispersions prepared at different temperatures with ethanol showed different X-ray diffraction patterns (III) (Fig. 12). The diffractogram of dispersion 10 exhibited no reflections, which means that the sample was entirely amorphous, whereas dispersion 80 included an amorphous part and reflections at 7.5°, 12.9°, 19.8° and 22.6° (2θ). The peak sites are characteristic for the single helical inclusion complex of amylose and ethanol—the Vh-type allomorph (Le Bail et al., 1995). Dispersion 40 was almost entirely amorphous with only two weak reflections at about 12.9° and 19.8° (Fig. 12). The higher crystallinity and tendency to complex formation with higher temperature are consistent with the result of a study of the effect of temperature on amylose–lipid complexes (Biliaderis and Galloway, 1989). The dispersion prepared at 40°C (dispersion 40) showed the best film forming properties and has been patented (Krogars et al., 2001). The favourable properties of this dispersion can be ascribed to an almost entirely amorphous nature and the smaller particle size than dispersion 10. Dispersion 80 had a particle size close to dispersion 40, but in the case of dispersion 80 the amylose-ethanol complex apparently disturbed the film forming.

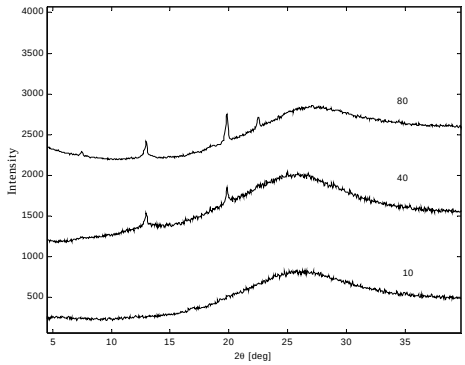

Fig. 12. X-ray diffraction patterns of dispersions prepared at different temperatures.

Figure 13 shows a close-up of the NIR spectra of amylose-rich starch films. The water band at around 1940 nm is caused by a combination of OH stretching and bending vibrations (Choppin and Downey, 1972). The peak location for film 40 is

at longer wavelengths compared to films 10 and 80, indicating that the water in film 40 is more strongly associated with the starch structure (i.e. there are more hydrogen bonds) (Delwiche, 1990).

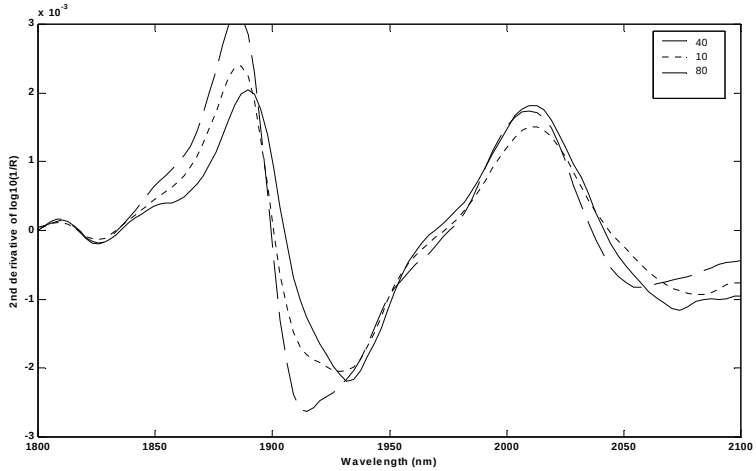

Figure 13. The effect of dispersion preparation temperature on second derivative spectra, 1800-2100 nm, of the subsequently prepared films.

5.2.3 Stability of amylose starch dispersion

Dispersion 40 was stored for nine months (III). During this time two new reflections emerged in the XRD pattern (Fig. 14). The four reflections in total, at 7.5°, 12.9°, 19.8° and 22.6° (2θ), are typical for amylose–ethanol complex (Vh-type). Amylose is responsible for the initial recrystallization (Smits et al., 1999) at least for the B-type lattice. The changes appearing in the XRD patterns are very small. The sensitivity of X-ray diffraction is low, however, relative to techniques such as solid state NMR and FT-IR. These other techniques that are capable of detecting even minor differences in crystallinity (Smits et al., 1998) would possibly have given more information about the crystal conformation. The changes occurring during nine months were minor, however. The relation between crystallinity and film forming ability needs to be studied in more detail.

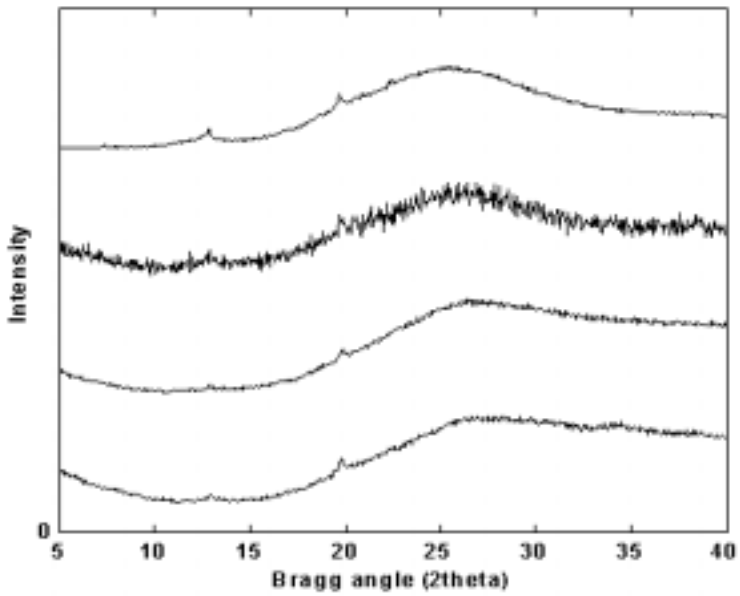

Figure 14. X-ray diffraction patterns of dispersion 40 stored for (bottom to top) 1 day, 2 days, 3 months and 9 months.

5.3 Free films prepared from amylose starch solution versus dispersion

Films were similar in appearance independently of the method of preparation, i.e. whether prepared from a hot solution or an ambient tempered dispersion (dispersion 40). The solution and the dispersion had the same content of amylose-rich starch and plasticizer mixture (sections 4.5.1 and 4.5.2). The crystallinity did not differ significantly for the prepared films and the tensile strength values were similar (Table 6). The only property that differed was the elongation value, which was almost twice as large for the dispersion-based films. The reason for this result is unclear. The results indicate, however, that the film formation is as good for the amylose starch dispersion as for the hot solution. The amorphous particles seem to merge with one another fully during the film formation, in spite of the relatively large particle size compared with commercial pseudolatex dispersions. Very few studies have compared solution and dispersion based film-forming agents. Gutierrez-Rocca and McGinity (1993) compared, however, the changes in mechanical properties during aging of acrylic resin copolymer films cast from aqueous dispersion and corresponding films cast from

organic solution. There was a decrease in elongation and increase in tensile strength during storage for both aqueous and organic solvent cast films.

Table 6. Mechanical properties and crystallinity of free films prepared of amylose-rich starch solution and dispersion.

	Solution	Dispersion 40
Tensile strength (MPa)	4 ± 1	5 ± 0
Elongation (%)	14 ± 2	26 ± 3
Crystallinity (%)	24	22

5.4 Effect of coating conditions on amylose starch coatings

5.4.1 Effect of temperature

In coating with the amylose starch solution, an increase in the temperature of the coating pan from 40°C to 70°C resulted in a decrease in surface roughness values especially with high spray rates (II). Thus, higher temperatures up to 70°C seem to produce a better quality, smoother amylose starch film coating. For the amylose starch dispersion, increasing temperature in the pan, up to approximately 50°C, produced smoother film coatings. The smoothness of the films did not increase further with increase in the temperature from 50ºC to 70ºC. At a coating temperature as low as 30ºC the tablets were prone to over-wet, which resulted in rougher film coatings (IV). The most suitable coating temperature for aqueous amylose starch dispersion, in a side-vented pan coating process, would thus seem to lie between 50 and 70°C. A suitable coating temperature for the solution coating would appear to be in the same range as for the dispersion coating when the spray rate is the same.

5.4.2 Effect of spray rate

The crushing strength of tablets coated with amylose starch was positively affected by the pan coating temperature, and negatively affected by the spray rate of the coating solution. At the lowest spray rate, however, the coating temperature had virtually no, or very little, effect on the crushing strength (II). This can be explained by the over-wetting of the film coatings, which is generally avoided at a lower spray rate, even at

low temperatures. With over-wetting avoided, film formation was enhanced. The present results also showed that there is a significant interaction between the coating temperature and the spray rate, which affects the mechanical strength of the coated tablets. Slowest drug release was obtained when both the temperature and the spray rate were at high levels. This indicates that these coating conditions were the most suitable as a short lag time is expected for a good coating due to the time required for swelling. Although there were differences in the drug release depending on the spray rate (and other variables) the drug release did not show sustained release character in any case. The coating conditions can affect the film thickness, and thereby indirectly the crushing strength (Fell et al., 1979) and dissolution results. The possible effects of the coating conditions on the tablet core must also be taken into consideration in evaluating the results.

5.4.3 Effect of atomizing air pressure

The atomizing air pressure had no effect on film coat thickness (i.e. tablet height) at medium and high temperatures of the coating pan (IV). However, the coat thickness of the tablets was higher at low coating temperature and high atomizing air pressure. As the atomizing air pressure increases it increased the surface area available for evaporation (Aulton and Twitchell, 1995), and the droplets dry faster and, as a consequence, the tablets are less over-wetted in comparison with tablets coated at lower atomizing air pressures. With the present aqueous amylose dispersions, however, the atomizing air pressure was found to be of minor importance. In contrast, atomizing air pressure has been found to be of importance in coating with aqueous cellulose coating solutions (Aulton et al., 1997).

6. CONCLUSIONS

1. Free films plasticized with a combination of sorbitol and glycerol are of greater stability than films plasticized with either of the polyols separately. The different size of the polyols may induce more interactions between the constituents, resulting in a more stable film.

2. In coating with amylose-rich maize starch solution, the process conditions (i.e. temperature and spray rate) and the amount of plasticizer should be chosen with care as they significantly influence the resulting coating.

3. With optimal coating conditions and plasticizer mixture content, amylose-rich maize starch solution forms a smooth coating. The need for special equipment for preparing the aqueous amylose starch coating solution and coating with heated solutions is a limitation of the technique.

4. Increasing the temperature used in the preparation of dispersions results in higher crystallinity and smaller particle/aggregate size. Lower crystallinity and smaller particle size are favourable for the film formation.

5. The aqueous-based dispersion that was developed forms continuous, flexible and transparent films.

6. Application of the new aqueous-based amylose-rich starch dispersion to tablets can be conducted without difficulty. The coating study verified that the dispersion produces smooth coatings, with suitable coating conditions, and that it is a rapidly releasing potential coating material for pharmaceutical dosage forms. Development work needs to be continued, however, in order to achieve a competitive coating material and long-term stability studies of amylose-rich starch coated tablets should be conducted.

REFERENCES

Abd Karim, A., Norziah, M.H., and Seow, C.C., 2000. Methods for the study of starch retrogradation. Food Chem., 71, 9-36.

Arvanitoyannis, I., Kalichevsky, M., Blanshard J.M.V., and Psomiadou, E., 1994. Study of diffusion and permeation of gases in undrawn and uniaxially drawn films made from potato and rice starch conditioned at different relative humidities. Carbohydr. Polym., 24, 1-15.

Arvanitoyannis, I., Psomiadou, E., and Nakayama, A., 1996. Edible films made from sodium caseinate, starches, sugars or glycerol. Part 1. Carbohydr. Polym., 31, 179-192.

Atwell, W.A., Hood, L.F., Lineback, D.R., Varriano-Marston, E., and Zobel, H.F., 1988. The terminology and methodology associated with basic starch phenomena. Cereal Foods World, 33, 306-311.

Aulton, M.E., Abdul-Razzak, M.H., and Hogan, J.E., 1981. The mechanical properties of hydroxypropylmethylcellulose films derived from aqueous systems. Part 1: The influence of plasticizers. Drug Dev. Ind. Pharm., 7, 649-668.

Aulton, M.E. and Twitchell, A.M., 1995. Film coat quality. In*: Pharmaceutical Coating Technology*. Hogan, G.J. and Aulton, M. (Eds.), Taylor & Francis cop., London, pp. 363-383.

Aulton, M.E., Twitchell, A.M., and Hogan, J.E., 1997. Physical properties of HPMC solutions and their role in the film coating process and the quality of coated product. In: *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. McGinity, J.W. (Ed.), Marcel Dekker Inc., New York, pp. 227-266.

Bader, H.G. and Göriz, D., 1994a. Investigation on high amylose corn starch films. Part 1: wide angle X-ray scattering (WAXS). Starch/Stärke, 46, 229-232.

Bader, H.G and Göritz, D., 1994b. Investigations on high amylose corn starch films. Part 3: stress strain behaviour. Starch/Stärke, 46, 435-439.

Biliaderis, C.G. and Galloway, G., 1989. Crystallization behaviour of amylose-V complexes: structure–property relationships. Carbohydr. Res., 189, 31-48.

Brown, G.L., 1956. Formation of films from polymer dispersions. J. Polym. Sci., 21, 423-434.

Buléon, A., Delage, M.M., Brisson, J., and Chanzy, H., 1990. Single crystals of V amylose complexed with isopropanol and acetone. Int. J. Biol. Macromol., 12, 25-33.

Choppin, G. and Downey, J., 1972. Near-infrared studies of the structure of water. IV. Water in relatively nonpolar solvents. J. Chem. Physics, 56, 5899-5904.

Curá, J.A., Jansson, P.-E., and Krisman, C.R., 1995. Amylose is not strictly linear. Starch/Stärke, 47, 207-209.

Dillon, R.E., Matheson, A., and Bradford, E.B., 1951. Sintering of synthetic latex particles. J. Colloid Sci., 6, 108-117.

Delwiche, S.R., 1990. The influence of water on the near infrared spectra of starch and cellulose, Ph.D. Thesis, Cornell University, Ithaca, USA.

Eckersley, S.T. and Rudin, A., 1990. Mechanism of film formation from polymer latexes. J. Coat. Tech., 62, 89-100.

Eckersley, S.T. and Rudin, A., 1994. The film formation of acrylic latexes: a comprehensive model of film coalescence. J. Appl. Polym. Sci., 53, 1139-1147.

Ellis, H.S. and Ring, S.G., 1985. A study of some factors influencing amylose gelation. Carbohydr. Polym., 5, 201-213.

Fanta, G.F., Felker, F.C., and Shogren, R.L., 2002. Formation of crystalline aggregates in slowly-cooled starch solutions prepared by steam jet cooking. Carbohydr. Polym., 48, 161-171.

Fell, J.T., Rowe, R.C., and Newton, J.M., 1979. The mechanical strength of film-coated tablets. J. Pharm. Pharmacol., 31, 69-72.

Felton, L.A. and McGinity, J.W., 1996. Influence of tablet hardness and hydrophobicity on the adhesive properties of an acrylic resin copolymer. Pharm. Dev. Technol., 1, 381-389.

Felton, L.A. and McGinity, J.W., 1997. Influence of plasticizers on the adhesive properties of an acrylic resin copolymer to hydrophilic and hydrophobic tablet compacts. Int. J. Pharm. 154, 167-178.

Forssell, P., Mikkilä, J., and Suortti, T., 1996. Plasticization of barley starch with glycerol and water. J.M.S.-Pure Appl. Chem., A33, 703-715.

Forssell, P.M., Mikkilä, J.M., Moates, G.K., and Parker, R., 1997. Phase and glass transition bahaviour of concentrated barley starch–glycerol–water mixtures, a model for thermoplastic starch. Carbohydr. Polym., 34, 275-282.

Forssell, P.M., Hulleman, S.H.D., Myllärinen, P.J., Moates, G.K., and Parker, R., 1999. Aging of rubbery thermoplastic barley and oat starches. Carbohydr. Polym., 39, 43-51.

Forssell, P., Lahtinen, R., Lahelin, M., and Myllärinen, P., 2002. Oxygen permeability of amylose and amylopectin films. Carbohydr. Polym., 47, 125-129.

French, A.D. and Zobel, H.F., 1967. X-ray diffraction of oriented amylose fibers. I. Amylose dimethyl sulfoxide complex. Biopolymers, 5, 457-464.

Friedman, R.B., DeBoer, E.D., Delgado, G.A., Furcsik, S.L., Qvyjt, F., and Tenbarge, F.L., 1999. Targeting of an appropriate amylose type starch for specific product applications. Macromol. Symp., 140, 81-91.

García, M.A., Martino, M.N., and Zaritzky, N.E., 1999. Edible starch films and coatings characterization: scanning electron microscopy, water vapor and gas permeabilities. Scanning, 21, 348-353.

García, M.A., Martino, M.N., and Zaritzky, N.E., 2000. Microstructural characterization of plasticized starch based films. Starch/Stärke, 52, 118-124.

Gaudin, S., Lourdin D., Le Botlan, D., Ilari, J.L., and Colonna, P., 1999. Plasticization and mobility in starch-sorbitol films. J. Cereal Sci., 29, 273-284.

Gidley, M.J., 1989. Molecular mechanisms underlying amylose aggregation and gelation. Macromolecules, 22, 351-358.

Gidley, M.J. and Bulpin, P.V., 1989. Aggregation of amylose in aqueous systems: the effect of chain length on phase behaviour and aggregation kinetics. Macromolecules, 22, 341-346.

Godet, M.C., Buléon, A., Tran, V., and Colonna, P., 1993. Structural features of fatty acid-amylose complexes. Carbohydr. Polym., 21, 91-95.

Gutierrez-Rocca, J.C. and McGinity, J.W., 1993. Influence of aging on the physical–mechanical properties of acrylic resin film cast from aqueous dispersions and organic solutions. Drug Dev. Ind. Pharm., 19, 315-332.

Haugaard, V.K., Udsen, A.-M., Mortensen, G., Høegh, L., Petersen, K., and Monahan, F., 2001. Potential food applications of biobased materials. An EU-concerted action project. Starch/Stärke, 53, 189-200.

Heinemann, C., Conde-Petit, B., Nuessli, J., and Escher, F., 2001. Evidence of starch inclusion complexation with lactones. J. Agric. Food Chem., 49, 1370-1376.

Heinämäki, J.H., Lehtola, V.-M., Nikupaavo, P., and Yliruusi, J.K., 1994. The mechanical and moisture permeability properties of aqueous-based hydroxypropyl methylcellulose coating systems plasticized with polyethylene glycol. Int. J. Pharm., 112, 191-196.

Heinämäki, J., Ruotsalainen, M., Lehtola, V.-M., Antikainen, O., and Yliruusi, J., 1997. Optimization of aqueous-based film coating of tablets performed by a side-vented pan coating system. Pharm. Dev. Tech., 2, 357-364.

Hinkle, M.E. and Zobel, H.F., 1968. X-ray diffraction of oriented amylose fibers. III. The structure of amylose-n-butanol complexes. Biopolymers, 6, 1119-1128.

Hulleman, S.H.D., Kalisvaart, M.G., Janssen, F.H.P., Feil, H., and Vliegenthart, J.F.G., 1999. Origins of B-type crystallinity in glycerol-plasticized, compression-moulded potato starches. Carbohydr. Polym., 39, 351-360.

Hutchings, D., Clarson, S., and Sakr, A., 1994. Studies of the mechanical properties of free films prepared using an ethylcellulose pseudolatex coating system. Int. J. Pharm., 104, 203-213.

Imberty, A., Chanzy, H., Pérez, S., Buléon, A., and Tran, V., 1988. The double-helical nature of the crystalline part of A-starch. J. Mol. Biol., 201, 365-378.

Imberty, A. and Perez, S., 1988. A revisit to the three-dimensional structure of B-type starch. Biopolymers, 27, 1205-1221.

Johnson, K., Hathaway, R., Leung, P., and Franz, R., 1991. Effect of triacetin and polyethylene glycol 400 on some physical properties of hydroxypropyl methylcellulose free films. Int. J. Pharm., 73, 197-208.

Kalichevsky, M.T., Jaroszkiewicz, E.M., and Blanshard, J.M.V., 1993. A study of the glass transition of amylopectin-sugar mixtures. Polymer, 34, 346-358.

Kester, J.J. and Fennema, O.R., 1986. Edible films and coatings: a review. Food Technol., 48, 47-59.

Krogars, K., Heinämäki, J., Yliruusi, J., Partanen, R., Myllärinen, P., and Forssell, P., 2001. Method for preparing an aqueous coating dispersion of starch and an aqueous coating dispersion of starch prepared by that method. Finnish Patent Application #20011017.

Kuutti, L., Peltonen, J., Myllärinen, P., Teleman, O., and Forssell, P., 1998. AFM in studies of thermoplastic starches during aging. Carbohydr. Polym., 37, 7-12.

Laitinen, N., Antikainen, O., and Yliruusi, J., 2002. Does a powder surface contain all necessary information for particle size distribution analysis? Eur. J. Pharm. Sci., 17, 217-227.

Le Bail, P., Bizot, H., and Buléon, A., 1993. B to A type phase transition in short amylose chains. Carbohydr. Polym., 21, 99-104.

Le Bail, P., Bizot, H., Pontoire, B., and Buléon, A., 1995. Polymorphic transitions of amylose-ethanol crystalline complexes induced by moisture exchanges. Starch/Stärke, 47, 229-232.

Leloup, L.M., Colonna, P., and Buléon, A., 1991. Influence of amylose–amylopectin ratio on gel properties. J. Cereal Sci., 13, 1-13.

Lin, S.-Y., Lee, C.-J., and Lin, Y.-Y., 1991. The effect of plasticizers on compatibility, mechanical properties, and adhesion strength of drug-free Eudragit E films. Pharm. Res., 8, 1137-1143.

Lourdin, D., Della Valle, G., and Colonna, P., 1995. Influence of amylose content on starch films and foams. Carbohydr. Polym., 27, 261-270.

Lourdin, D., Bizot, H., and Colonna P., 1997a. Antiplasticization in starch–glycerol films? J. Appl. Polym. Sci., 63, 1047-1053.

Lourdin, D., Coignard, L., Bizot, H., and Colonna, P., 1997b. Influence of equilibrium relative humidity and plasticizer concentration on the water content and glass transition of starch materials. Polymer, 38, 5401-5406.

Lourdin, D., Colonna, P., Brownsey, G.J., Noel, T.R., and Ring, S.G., 2002. Structural relaxation and physical ageing of starchy materials. Carbohydr. Res., 337, 827-833.

Manners, D.J., 1989. Recent developments in our understanding of amylopectin structure. Carbohydr. Polym., 11, 87-112.

Mark, A.M., Roth, W.B., Mehltretter, C.L., and Rist, C.E., 1966. Oxygen permeability of amylomaize starch films. Food Technol., 20, 75-77.

Milojevic, S., Newton, J.M., Cummings, J.H., Gibson, G.R., Bothman, R.L., Ring, S.G., Allwood, M.C., and Stockham, M., 1995. Amylose, the new prespective in oral drug delivery to the human large intestine. S.T.P. Pharm. Sci., 5, 47-53.

Milojevic, S., Newton, J.M., Cummings, J.H., Gibson, G.R., Botham, R.L, Ring, S.G., Stockham, M., and Allwood, C., 1996a. Amylose as a coating for drug delivery to the colon: preparation and in vitro evaluation using 5-aminosalicylic acid pellets. J. Contr. Rel., 38, 75-84.

Milojevic, S., Newton, J.M., Cummings, J.H., Gibson, G.R., Botham, R.L., Ring, S.G., Stockham, M., and Allwood, M.C., 1996b. Amylose as a coating for drug delivery to the colon: preparation and in vitro evaluation using glucose pellets. J. Contr. Rel., 38, 85-94.

Morrison, W.R., Law, R.V., and Snape, C.E., 1993. Evidence for inclusion complexes of lipids with V-amylose in maize, rice and oat starches. J. Cereal Sci., 18, 107-109.

Myllärinen, P., Buleon, A., Lahtinen, R., and Forssell, P., 2002a. The crystallinity of amylose and amylopectin films. Carbohydr. Polym., 48, 41-48.

Myllärinen, P., Partanen, R., Seppälä, J., and Forssell, P., 2002b. Effect of glycerol on behaviour of amylose and amylopectin films. Carbohydr. Polym., 50, 355-361.

Nagai, T., Obara, S., Kokubo, H., and Hoshi, N., 1997. Application of HPMC and HPMCAS to aqueous film coating of pharmaceutical dosage forms. In: *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms.* McGinity, J.W. (Ed.), Marcel Dekker Inc., New York, pp. 177-225.

Nagarsenker, M.S. and Hegde, D.D., 1999. Optimization of the mechanical properties and water-vapor transmission properties of free films of hydroxypropylmethylcellulose. Drug Dev. Ind. Pharm., 25, 95-98.

Obara, S. and McGinity, J.W., 1994. Properties of free films prepared from aqueous polymers by a spraying technique. Pharm. Res., 11, 1562-1567.

Obara, S. and McGinity, J.W., 1995. Influence of processing variables on the properties of free films prepared from aqueous polymeric dispersions by a spray technique. Int. J. Pharm. 126, 1-10.

Palviainen, P., Heinämäki, J., Myllärinen, P., Lahtinen, R., Yliruusi, J., and Forssell, P., 2001. Corn starches as film formers in aqueous-based film coating. Pharm. Dev. Tech., 6, 351-359.

Parikh, N.H., Porter, S.C., and Rohera, B.D., 1993. Aqueous ethylcellulose dispersion of ethylcellulose. I. Evaluation of coating process variables. Pharm. Res., 10, 525-534.

Polaczek, E., Starzyk, F., and Tomasik, P., 1999. Starch–alcohol complexes. Carbohydr. Polym., 39, 37-42.

Rappenecker, G. and Zugenmaier, P., 1981. Detailed refinement of the crystal structure of V_h-amylose. Carbohydr. Res., 89, 11-19.

Reiland, T.L. and Eber, A.C., 1986. Aqueous gloss solutions: formula and process variables effects on the surface texture of film coated tablets. Drug Dev. Ind. Pharm., 12, 231-245.

Rindlav, Å., Hulleman, S.H.D., and Gatenholm, P., 1997. Formation of starch films with varying crystallinity. Carbohydr. Polym., 34, 25-30.

Rindlav-Westling, Å., Stading, M., Hermansson, A.-M., and Gatenholm, P., 1998. Structure, mechanical and barrier properties of amylose and amylopectin films. Carbohydr. Polym., 36, 217-224.

Rindlav-Westling, Å., Stading, M., and Gatenholm, P., 2002. Crystallinity and morphology in films of starch, amylose and amylopectin blends. Biomacromolecules, 3, 84-91.

Roman, M.-C. and Fulper, D., 2000. Migration of polyol plasticizers in soft gelatin capsules. AAPS Pharm. Sci., 2, Abstract 95.

Roos, Y.H., 1995. *Phase Transitions in Foods.* Academic Press, Inc., San Diego, 360 p.

Rowe, R.C., 1978. The effect of some formulation and process variables on the surface roughness of film coated tablets. J. Pharm. Pharmacol., 30, 669-672.

Rowe, R.C. and Forse, S.F., 1982. The effect of process conditions on the incidence of bridging of the intagliations and edge splitting and peeling on film coated tablets. Acta Pharm. Technol., 28, 207-210.

Ruotsalainen, M., 2003. Studies on aqueous film coating of tablets performed in a side-vented pan coater. Ph.D. Thesis. University of Helsinki, Helsinki, Finland.

Sastry, S.V., Wilber, W., Reddy, I.K., and Khan, M.A., 1998. Aqueous-based polymeric dispersion: preparation and characterization of cellulose acetate pseudolatex. Int. J. Pharm., 165, 175-189.

Shogren, R.L., 1992. Effect of moisture content on the melting and subsequent physical aging of cornstarch. Carbohydr. Polym., 19, 83-90.

Siew, L.F., Basit, A.W., and Newton, J.M., 2000a. The properties of amylose–ethyl cellulose films cast from organic-based solvents as potential coatings for colonic drug delivery. Eur. J. Pharm. Sci., 11, 133-139.

Siew, L.F., Basit, A.W., and Newton, J.M., 2000b. The potential of organic-based amylose–ethyl cellulose film coatings as oral colon-specific drug delivery systems. AAPS PharmSciTech, 1(3), http://www.pharmscitech.com/.

Smits, A.L.M., Ruhnau, F.C., Vliegenthart, J.F.G., and Van Soest, J.J.G., 1998. Aging of starch based systems as observed with FT-IR and solid state NMR spectroscopy. Starch/Stärke, 50, 478-483.

Smits, L.M, Hulleman, S.H.D., Van Soest, J.J.G., Feil, H., and Vliegenhart, F.G., 1999. The influence of polyols on the molecular organization in starch-based plastics. Polym. Adv. Technol., 10, 570-573.

van Soest, J.J.G., Benes, K., de Wit, D., and Vliegenthart, J.F.G., 1996. The influence of starch molecular mass on the properties of extruded thermoplastic starch. Polymer, 37, 3543-3552.

van Soest, J.J.G. and Borger, D.B., 1997. Structure and properties of compression-molded thermoplastic starch materials from normal and high amylose maize starches. J. Appl. Polym. Sci., 64, 631-644.

van Soest, J.J.G. and Essers, P., 1997. Influence of amylose–amylopectin ratio on properties of extruded starch plastic sheets. J.M.S.-Pure Appl. Chem., A34, 1665-1689.

van Soest, J.J.G. and Knooren, N., 1997. Influence of glycerol and water content on the structure and properties of extruded starch plastic sheets during aging. J. Appl. Polym. Sci., 64, 1411-1421.

Stading, M., Rindlav-Westling, Å., and Gatenholm, P., 2001. Humidity-induced structural transitions in amylose and amylopectin films. Carbohydr. Polym., 45, 209-217.

Swinkels, J.J.M., 1985. Sources of starch, its chemistry and physics. In: *Starch Conversion Technology*. van Beynum, G.M.A. and Roels, J.A. (Eds.) Marcel Dekker Inc., New York, pp.15-46.

Takeo, K., Tokumura, A., and Kuge, T., 1973. Complexes of starch and its related materials with organic compounds. Starch/Stärke, 25, 357-362.

Twitchell, A.M., Hogan, J.E., and Aulton, M.E., 1995. The behaviour of film coating droplets on their impigement onto uncoated and coated tablets. S.T.P. Pharm. Sci., 5, 190-195.

Voyutski, S.S., 1958. Amendment to the papers by Bradford, Brown, and co-workers: “concerning mechanism of film formation from high polymer dispersions”. J. Polym. Sci., 32, 528-530.

Westhoff, R.P., Kwolek, W.F., and Otey, F.H., 1979. Starch–polyvinyl alcohol films–effect of various plasticizers. Starch/Stärke, 5, 163-165.

Wolff, I.A., Davis, H.A., Cluskey, J.E., Gundrum, L.J., and Rist, C.E., 1951. Preparation of films from amylose. Ind. Eng. Chem., 43, 915-919.

Wu, H.-C.H. and Sarko, A., 1978. The double-helical molecular structure of crystalline B-amylose. Carbohydr. Res., 61, 7-25.